

AMENDMENTS TO THE CLAIMS:

Please amend the claims as follows:

1. (Currently Amended) An isolated HBV polynucleic acid comprising a reverse transcriptase encoding domain, said reverse transcriptase encoding domain comprising a serine encoding codon at position 204.

2. (Currently Amended) The HBV polynucleic acid according to claim 1, said reverse transcriptase encoding domain further comprising a methionine encoding codon at position 180.

3. (Previously Presented) The HBV polynucleic acid according to claim 1 which is defined by SEQ ID NO:6 or the complement thereof.

4. (Previously Presented) An isolated HBV DNA polymerase/reverse transcriptase protein, said protein comprising a reverse transcriptase domain, said reverse transcriptase domain comprising a serine at position 204 of the HBV reverse transcriptase domain.

5. (Previously Presented) The HBV DNA polymerase/reverse transcriptase protein according to claim 4 wherein said reverse transcriptase domain further comprises a methionine at position 180 of the HBV reverse transcriptase domain.

6. (Previously Presented) An isolated HBV DNA polymerase/reverse transcriptase protein encoded by the isolated HBV polynucleic acid according to one of claims 1 to 3.

7. (Previously Presented) The HBV DNA polymerase/reverse transcriptase protein according to claim 4 which is defined by-SEQ ID NO:4.

8. (Previously Presented) An isolated HBV variant comprising a polynucleic acid according to claim 1.

9. (Previously Presented) An isolated HBV variant comprising a protein according to claim 4.

10. (Previously Presented) A vector comprising the HBV polynucleic acid according to claim 1.

11. (Previously Presented) A host cell comprising the HBV polynucleic acid according to claim 1, a variant Hepatitis B virus containing said polynucleic acid or a vector containing said polynucleic acid.

12. (Previously Presented) A host cell comprising the HBV DNA polymerase/reverse transcriptase protein according to claim 4 or a variant Hepatitis B virus containing said HBV DNA polymerase/reverse transcriptase protein.

13. (Currently Amended) A method for detecting the presence of an HBV in a biological sample, said method comprising the step of detecting the presence of an HBV polynucleic acid comprising a reverse transcriptase encoding domain, said reverse transcriptase encoding domain comprising a serine encoding codon at position 204.

14. (Currently Amended) The method according to claim 13 comprising:

(i) obtaining a target HBV polynucleic acid from said biological sample wherein said target HBV polynucleic acid is suspected to comprise a serine-encoding codon at position 204 of the HBV reverse transcriptase domain or to comprise a methionine-encoding codon at position 180 and a serine-encoding codon at position 204 of the HBV reverse transcriptase domain;

(ii) obtaining the nucleic acid sequence of the target HBV polynucleic acid of (i);

(iii) inferring, from the nucleic acid sequence obtained in (ii), the presence of said serine-encoding codon at position 204 of the HBV reverse transcriptase domain or of said methionine-encoding codon at position 180 and said serine-encoding codon at position 204 of the HBV reverse transcriptase domain and, therefrom, the presence of said HBV in said biological sample.

15. (Currently Amended) The method according to claim 13 comprising:

(i) obtaining a target HBV polynucleic acid from said biological sample wherein said target HBV polynucleic acid is suspected to comprise a serine-encoding codon at position 204 of the HBV reverse transcriptase domain or to comprise a methionine-encoding codon at position 180 and a serine-encoding codon at position 204 of the HBV reverse transcriptase domain;

(ii) contacting the target HBV polynucleic acid of (i) with an oligonucleotide capable of discriminating a codon at position 204 encoding a serine from a codon at position 204 encoding a methionine, valine or isoleucine resulting in a discriminatory signal relating to codon at position 204, or with an oligonucleotide capable of discriminating a codon at position 180 encoding a methionine from a codon at position 180 encoding a leucine resulting in a discriminatory signal relating to codon at position 180 and an oligonucleotide capable of discriminating a codon at position 204 encoding a serine from a codon at position 204 encoding a methionine, valine or isoleucine resulting in a discriminatory signal relating to codon at position 204;

(iii) inferring, from the discriminatory signal obtained in (ii), the presence of said serine-encoding codon at position 204 of the HBV reverse transcriptase or of said methionine-encoding codon at position 180 and said serine-encoding codon at position 204 of the HBV reverse transcriptase domain and, therefrom, the presence of said HBV in said biological sample.

16. (Original) The method according to claim 15 wherein said discriminating in (ii) is based on hybridization and wherein said discriminatory signal in (iii) is a hybridization signal.

17. (Currently Amended) A method for detecting resistance to lamivudine or a combination of antiviral drugs comprising lamivudine of an HBV virus present in a biological sample, said method comprising the step of detecting the presence of an HBV polynucleic acid comprising a reverse transcriptase encoding domain, said reverse transcriptase encoding domain comprising a serine encoding codon at position 204.

18. (Currently Amended) The method according to claim 17 comprising:

(i) obtaining a target HBV polynucleic acid from said biological sample wherein said target HBV polynucleic acid is suspected to comprise a serine-encoding codon at position 204 of the HBV reverse transcriptase domain or to comprise a methionine-encoding codon at position 180 and a serine-encoding codon at position 204 of the HBV reverse transcriptase domain;

(ii) obtaining the nucleic acid sequence of the target HBV polynucleic acid of (i);

(iii) inferring, from the nucleic acid sequence obtained in (ii), the presence of said serine-encoding codon at position 204 in the HBV reverse transcriptase domain or of

said methionine-encoding codon at position 180 and said serine-encoding codon at position 204 in the HBV reverse transcriptase domain and, therefrom, said resistance to lamivudine or a combination of antiviral drugs comprising lamivudine of an HBV virus present in said biological sample.

19. (Currently Amended) The method according to claim 17 comprising:

(i) obtaining a target HBV polynucleic acid from said biological sample wherein said target HBV polynucleic acid is suspected to comprise a serine-encoding codon at position 204 of the HBV reverse transcriptase domain or to comprise a methionine-encoding codon at position 180 and a serine-encoding codon at position 204 of the HBV reverse transcriptase domain;

(ii) contacting the target HBV polynucleic acid of (i) with an oligonucleotide capable of discriminating a codon at position 204 encoding a serine from a codon at position 204 encoding a methionine, valine or isoleucine resulting in a discriminatory signal relating to codon at position 204,

or with an oligonucleotide capable of discriminating a codon at position 180 encoding a methionine from a codon at position 180 encoding a leucine resulting in a discriminatory signal relating to codon at position 180 and an oligonucleotide capable of discriminating a codon at position 204 encoding a serine from a codon at position 204 encoding a methionine, valine or isoleucine resulting in a discriminatory signal relating to codon at position 204;

(iii) inferring, from the discriminatory signal obtained in (ii), the presence of said serine-encoding codon at position 204 in the HBV reverse transcriptase domain or of

said-methionine-encoding codon 180 and said serine-encoding codon at position 204 in the HBV reverse transcriptase domain and, therefrom, said resistance to lamivudine or a combination of antiviral drugs comprising lamivudine of an HBV virus present in said biological sample.

20. (Original) The method according to claim 19 wherein said discriminating in (ii) is based on hybridization and wherein said discriminatory signal in (iii) is a hybridization signal.

21. (Currently Amended) A diagnostic kit for detecting the presence of an HBV in a biological sample, said kit comprising a means for detecting the presence of an HBV polynucleic acid comprising a reverse transcriptase encoding domain, said reverse transcriptase encoding domain comprising a serine encoding codon at position 204.

22. (Currently Amended) The diagnostic kit according to claim 21 comprising:

(i) optionally, a means for obtaining the nucleic acid sequence of a target HBV polynucleic acid suspected to comprise a serine-encoding codon at position 204 of the HBV reverse transcriptase domain or to comprise a methionine-encoding codon at position 180 and a serine-encoding codon at position 204 of the HBV reverse transcriptase domain; and

(ii) a means for inferring, from the nucleic acid sequence obtained in (i), the presence of said serine-encoding codon at position 204 of the HBV reverse transcriptase domain or of said methionine-encoding codon at position 180 and said serine-encoding codon at position 204 of the HBV reverse transcriptase domain and, therefrom, the presence in said biological sample of said HBV.

23. (Original) The diagnostic kit according to claim 21 comprising an oligonucleotide capable of discriminating, in said HBV polynucleic acid, a codon 204 encoding a serine from a codon 204 encoding a methionine, valine or isoleucine.

24. (Original) The diagnostic kit according to claim 23 further comprising an oligonucleotide capable of discriminating, in said HBV polynucleic acid, a codon 180 encoding a methionine from a codon 180 encoding a leucine.

25. (Currently Amended) A diagnostic kit for detecting resistance to lamivudine or a combination of antiviral drugs comprising lamivudine of an HBV virus present in a biological sample, said kit comprising a means for detecting the presence of an HBV polynucleic acid comprising a reverse transcriptase encoding domain, said reverse transcriptase encoding domain comprising a serine encoding codon at position 204.

26. (Currently Amended) The diagnostic kit according to claim 25 comprising:
(i) optionally, a means for obtaining the nucleic acid sequence of the target HBV polynucleic acid suspected to comprise a serine-encoding codon at position 204 of the HBV reverse transcriptase domain or to comprise a methionine-encoding codon at position 180 and a serine-encoding codon at position 204 of the HBV reverse transcriptase domain; and

(ii) a means for inferring, from the nucleic acid sequence obtained in (i), the presence of said serine-encoding codon at position 204 in the HBV reverse transcriptase domain or of said methionine-encoding codon at position 180 and said serine-encoding codon at position 204 in the HBV reverse transcriptase domain and,

therefrom, resistance to lamivudine or a combination of antiviral drugs comprising lamivudine of an HBV virus present in said biological sample.

27. (Original) The diagnostic kit according to claim 25 comprising an oligonucleotide capable of discriminating, in said HBV polynucleic acid, a codon 204 encoding a serine from a codon 204 encoding a methionine, valine or isoleucine.

28. (Original) The diagnostic kit according to claim 27 further comprising an oligonucleotide capable of discriminating, in said HBV polynucleic acid, a codon 180 encoding a methionine from a codon 180 encoding a leucine.

29. (Previously Presented) The diagnostic kit according to claim 27 further comprising a means for detecting a discriminatory signal obtained by contacting said HBV polynucleic acid and said oligonucleotide.

30. (Previously Presented) The diagnostic kit according to claim 27 wherein said oligonucleotide is attached or immobilized to a solid support.

31. (Withdrawn) A method for detecting resistance to lamivudine or a combination of antiviral drugs comprising lamivudine of an HBV virus present in a biological sample, said method comprising the step of detecting the presence of an HBV DNA polymerase/reverse transcript protein, said protein comprising a reverse transcriptase domain, said reverse transcriptase domain comprising a serine at position 204 of the HBV reverse transcriptase domain.

32. (Withdrawn – Currently Amended) A method for screening for drugs active against an HBV virus comprising a polynucleic acid comprising a reverse transcriptase encoding domain, said reverse transcriptase encoding domain comprising a serine

encoding codon at position 204 or comprising a protein, wherein said protein comprises a reverse transcriptase domain and said reverse transcriptase domain comprises a serine at position 204 of the HBV reverse transcriptase domain, or said protein comprises a reverse transcriptase domain and said reverse transcriptase domain comprises a serine at position 204 and a methionine at position 180 of the HBV reverse transcriptase domain, or said protein comprises an amino acid sequence represented by SEQ ID NO:4, said method comprising:

- (i) measuring replication of said HBV virus in the absence of said drug;
- (ii) measuring replication of said HBV virus in the presence of said drug;
- (iii) inferring from (i) and (ii) the inhibitory effect of said drug on replication of said HBV virus.

33. (Withdrawn) The method according to claim 32 further comprising performing steps (i), (ii) and (iii) with a wild-type HBV virus and comparing the inhibitory effect of said drug on replication of said wild-type HBV virus with the inhibitory effect of said drug on replication of the HBV virus comprising the polynucleic acid or comprising a DNA polymerase/reverse transcriptase protein encoded by said polynucleic acid.

34. (Withdrawn – Currently Amended) A method for screening for drugs active against an HBV virus comprising a polynucleic acid comprising a reverse transcriptase encoding domain, said reverse transcriptase encoding domain comprising a serine encoding codon at position 204 or comprising a protein encoded by said polynucleic acid, said method comprising:

(i) measuring a DNA polymerase/reverse transcriptase activity of said HBV virus in the absence of said drug;

(ii) measuring the same DNA polymerase/reverse transcriptase activity as in (i) of said HBV virus in the presence of said drug;

(iii) inferring from (i) and (ii) the inhibitory effect of said drug on said DNA polymerase/reverse transcriptase activity of said HBV virus.

35. (Withdrawn) The method according to claim 34 further comprising performing steps (i), (ii) and (iii) with a wild-type HBV virus and comparing the inhibitory effect of said drug on said DNA polymerase/reverse transcriptase activity of said wild-type HBV virus with the inhibitory effect of said drug on said DNA polymerase/reverse transcriptase activity of the HBV virus comprising said polynucleic acid or comprising said DNA polymerase/reverse transcriptase protein.

Claim 36. (Canceled)

Claim 37 (Canceled)

38. (Previously Presented) The diagnostic kit according to claim 28 further comprising a means for detecting a discriminatory signal obtained by contacting said HBV polynucleic acid and said oligonucleotide capable of discriminating, in said HBV polynucleic acid, a codon 204 encoding a serine from a codon 204 encoding a methionine, valine or isoleucine and means for detecting a discriminatory signal obtained by contacting said HBV polynucleic acid and said oligonucleotide capable of discriminating, in said HBV polynucleic acid, a codon 180 encoding a methionine from a codon 180 encoding a leucine.

39. (Previously Presented) The diagnostic kit according to claim 28 wherein at least one of

said oligonucleotide capable of discriminating, in said HBV polynucleic acid, a codon 204 encoding a serine from a codon 204 encoding a methionine, valine or isoleucine is attached or immobilized to a solid support and

said oligonucleotide capable of discriminating, in said HBV polynucleic acid, a codon 180 encoding a methionine from a codon 180 encoding a leucine is attached or immobilized to a solid support.

40. (Currently Amended) A method for screening for drugs active against an HBV virus comprising a polynucleic acid comprising a reverse transcriptase encoding domain, said reverse transcriptase encoding domain comprising a serine encoding codon at position 204 or comprising a protein encoded by said polynucleic acid, said method comprising:

- (i) measuring replication of said HBV virus in the absence of said drug;
- (ii) measuring replication of said HBV virus in the presence of said drug; and
- (iii) inferring from (i) and (ii) the inhibitory effect of said drug on replication of said HBV virus.